General

Guideline Title

WHO guidelines for screening and treatment of precancerous lesions for cervical cancer prevention.

Bibliographic Source(s)

World Health Organization (WHO). WHO guidelines for screening and treatment of precancerous lesions for cervical cancer prevention. Geneva (Switzerland): World Health Organization (WHO); 2013. 40 p. [20 references]

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Recommendations

Major Recommendations

The definitions for the strength of the recommendations (strong, conditional) and the quality of evidence (high [++++], moderate [+++0], low [++00], and very low [+000]) are provided at the end of the "Major Recommendations" field.

Recommendation 1

The expert panel recommends against the use of cold knife conization (CKC) as treatment in a screen-and-treat strategy (strong recommendation, +000 evidence).

Remarks

The screen-and-treat strategies considered by the panel with CKC as treatment included a human papillomavirus (HPV) test, visual inspection with acetic acid (VIA), or an HPV test followed by VIA as screening. Although the benefits were similar for CKC compared with cryotherapy or loop electrosurgical excision procedure (LEEP) for all screen-and-treat strategies, the harms were greater with CKC. This recommendation applies to women regardless of human immunodeficiency virus (HIV) status. See Supplemental material, Sections A and B (see the "Availability of Companion Documents" field).

Recommendation 2

Where resources permit, the expert panel suggests a strategy of screen with an HPV test and treat with cryotherapy (or LEEP when not eligible for cryotherapy) over a strategy of screen with VIA and treat with cryotherapy (or LEEP when not eligible) (conditional recommendation, +000 evidence).

In resource-constrained settings, where screening with an HPV test is not feasible, the expert panel suggests a strategy of screen with VIA and treat with cryotherapy (or LEEP when not eligible) over a strategy of screen with an HPV test and treat with cryotherapy (or LEEP when not eligible) (conditional recommendation, +000 evidence).

Remarks

The benefits of screen-and-treat with an HPV test or VIA, compared to no screening, outweighed the harms, but the reductions in cancer and related mortality were greater with an HPV test when compared to VIA. The availability of HPV testing is resource-dependent and, therefore, the expert panel suggests that an HPV test over VIA be provided where it is available, affordable, implementable, and sustainable over time. This recommendation applies to women regardless of HIV status. See Supplemental material, Sections A and B (see the "Availability of Companion Documents" field).

Recommendation 3

The expert panel suggests a strategy of screen with an HPV test and treat with cryotherapy (or LEEP when not eligible for cryotherapy) over a strategy of screen with cytology followed by colposcopy (with or without biopsy) and treat with cryotherapy (or LEEP when not eligible) (conditional recommendation, +000 evidence).

Remarks

The reductions in cancer and related mortality were slightly greater with an HPV test only compared to cytology followed by colposcopy. Although there may be overtreatment of populations with high HPV prevalence and consequently more harms, as well as fewer cancers seen at first-time screening with an HPV test, there are greater resources required in cytology programmes due to quality control, training, and waiting time. The addition of colposcopy also requires a second visit. However, in countries where an appropriate/high-quality screening strategy with cytology (referring women with ASCUS [atypical squamous cells of undetermined significance] or greater results) followed by colposcopy already exists, either an HPV test or cytology followed by colposcopy could be used. See Supplemental material, Sections A and B (see the "Availability of Companion Documents" field).

Recommendation 4

The expert panel recommends a strategy of screen with VIA and treat with cryotherapy (or LEEP when not eligible for cryotherapy) over a strategy of screen with cytology followed by colposcopy (with or without biopsy) and treat with cryotherapy (or LEEP when not eligible) (strong recommendation, +000 evidence).

Remarks

The benefits and harms of the two screen-and-treat strategies are similar, but there are fewer harms with cytology followed by colposcopy with biopsy when indicated. Despite overtreatment with VIA and fewer cancers detected at first-time screening, more resources are required for cytology programmes with colposcopy (with or without biopsy) due to quality control, training, and waiting time, as well as a second visit. The recommendation for VIA over cytology followed by colposcopy can be applied in countries that are currently considering either strategy, or countries that currently have both strategies available. This recommendation applies to women regardless of HIV status. See Supplemental material, Sections A and B (see the "Availability of Companion Documents" field).

Recommendation 5

The expert panel suggests a strategy of screen with an HPV test and treat with cryotherapy (or LEEP when not eligible for cryotherapy) over a strategy of screen with an HPV test followed by colposcopy (with or without biopsy) and treat with cryotherapy (or LEEP when not eligible) (conditional recommendation, +000 evidence).

Remarks

The reductions in cancer and related mortality with either strategy outweigh the harms and costs of no screening, and were similar between the two strategies. Although overtreatment and, consequently, harms are reduced with the addition of colposcopy (with or without biopsy), there are more resource implications with colposcopy due to increased training of providers, quality control, waiting time, and the potential for more women to be lost to follow-up. The addition of colposcopy to an HPV test would also require a second visit. In countries without an existing screening strategy, an HPV test followed by colposcopy is not recommended. This recommendation applies to women regardless of HIV status. See Supplemental material, Sections A and B (see the "Availability of Companion Documents" field).

Recommendation 6

The expert panel suggests either a strategy of screen with an HPV test followed by VIA and treat with cryotherapy (or LEEP when not eligible for cryotherapy) or a strategy of screen with an HPV test and treat with cryotherapy (or LEEP when not eligible) (conditional recommendation, +000 evidence).

Remarks

The reductions in cancer and related mortality were greater with an HPV test used as a single screening test than with an HPV test followed by VIA, and this reduction was even greater in women of HIV-positive status. However, there may be overtreatment, and thus potentially greater harms with screen-and-treat when using an HPV test as a single test. There is also some uncertainty about the effects of an HPV test followed by VIA and how VIA performs after a positive HPV test because there was no direct evidence about this strategy. There is also the potential for additional resources that are required to refer women for VIA testing after a positive HPV test, the need for a second visit to perform VIA, and increased training to perform both tests. For these reasons, the recommendation is for either an HPV test followed by VIA or an HPV test only, and it is conditional. It is to be noted that benefits are more pronounced compared to harm in women of HIV-positive status when using an HPV test only. See Supplemental material, Sections A and B (see the "Availability of Companion Documents" field).

Recommendation 7

The expert panel suggests a strategy of screen with an HPV test followed by VIA and treat with cryotherapy (or LEEP when not eligible for cryotherapy) over a strategy of screen with VIA and treat with cryotherapy (or LEEP when not eligible) (conditional recommendation, +000 evidence).

Remarks

The reductions in cancer and related mortality with an HPV test followed by VIA or with VIA alone outweighed the harms. However, the harms may be greater when using VIA only, which is likely due to overtreatment. A slightly larger number of cancers may be detected on initial screen with VIA only. This recommendation is conditional due to the uncertain costs of providing the sequence of two tests (HPV test followed by VIA) over the single VIA test. In countries where an HPV test is not available, the expert panel suggests screening with VIA only. This recommendation applies to women regardless of HIV status. See Supplemental material, Sections A and B (see the "Availability of Companion Documents" field).

Recommendation 8

The expert panel suggests a strategy of screen with an HPV test followed by VIA and treat with cryotherapy (or LEEP when not eligible for cryotherapy) over a strategy of screen with cytology followed by colposcopy (with or without biopsy) and treat with cryotherapy (or LEEP when not eligible) (conditional recommendation, +000 evidence).

Remarks

The benefits of the two screen-and-treat strategies are similar. However, there may be higher resources required in cytology programmes due to quality control, training, and waiting time. The addition of colposcopy requires a second visit. This recommendation applies to women regardless of HIV status. See Supplemental material, Sections A and B (see the "Availability of Companion Documents" field).

Recommendation 9

The expert panel suggests a strategy of screen with an HPV test followed by VIA and treat with cryotherapy (or LEEP when not eligible for cryotherapy) over a strategy of screen with an HPV test followed by colposcopy (with or without biopsy) and treat with cryotherapy (or LEEP when not eligible) (conditional recommendation, +000 evidence).

Remarks

The reductions in cancer and related mortality of screen-and-treat with an HPV test followed by colposcopy (with or without biopsy) may be slightly greater compared to an HPV test followed by VIA. The panel agreed that the benefits of either strategy outweigh the harms and costs; however, the difference in costs between the strategies is uncertain. There may be more resource implications with colposcopy due to increased training of providers, quality control, waiting time, and the potential for more women to be lost to follow-up. It is also unclear whether women would perceive a difference between VIA and colposcopy; however, a biopsy during colposcopy may be less acceptable than VIA. This recommendation applies to women regardless of HIV status. See Supplemental material, Sections A and B (see the "Availability of Companion Documents" field).

Definitions

Grading of Recommendations Assessment, Development and Evaluation (GRADE) Categories of Quality of Evidence

High (++++): Further research is very unlikely to change confidence in the estimate of effect.

Moderate (+++0): Further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate.

Low (++00): Further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate.

Very low (+000): The Guideline Development Group (GDG) is very uncertain about the estimate.

Strength of Recommendations

- Strong: A strong recommendation means that it was clear to the panel that the net desirable consequences of the specified strategy outweighed those of the alternative strategy.
- Conditional: A conditional recommendation was made when it was less clear whether the net desirable consequences of the specified strategy outweighed those of the other strategy.

Interpretation of Strong and Conditional Recommendations

Implications	Strong recommendation "The expert panel recommends… "	Conditional recommendation "The expert panel suggests… "
For patients	Most individuals in this situation would want the recommended course of action, and only a small proportion would not. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.	The majority of individuals in this situation would want the suggested course of action, but many would not.
For clinicians	Most individuals should receive the intervention. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator.	Clinicians should recognize that different choices will be appropriate for each individual and that clinicians must help each individual arrive at a management decision consistent with his or her values and preferences. Decision aids may be useful to help individuals make decisions consistent with their values and preferences.
For policymakers	The recommendation can be adopted as policy in most situations.	Policy-making will require substantial debate and involvement of various stakeholders.

Clinical Algorithm(s)

The following clinical algorithms are available in the Annexes 2 and 3 of the original guideline document:

- Decision-making flowchart for screen-and-treat strategies
- Flowcharts for screen-and-treat strategies (negative or unknown HIV status)
    - Screen with an HPV test and treat with cryotherapy, or LEEP when not eligible for cryotherapy
    - Screen with an HPV test followed by VIA and treat with cryotherapy, or LEEP when not eligible for cryotherapy
    - Screen with VIA and treat with cryotherapy, or LEEP when not eligible for cryotherapy
    - Screen with an HPV test followed by colposcopy (with or without biopsy) and treat with cryotherapy, or LEEP when not eligible for cryotherapy
    - Screen with cytology followed by colposcopy (with or without biopsy) and treat with cryotherapy, or LEEP when not eligible for cryotherapy
- Flowcharts for screen-and-treat strategies (HIV-positive status or unknown HIV status in areas with high endemic HIV infection)
    - Screen with an HPV test and treat with cryotherapy, or LEEP when not eligible for cryotherapy
    - Screen with an HPV test followed by VIA and treat with cryotherapy, or LEEP when not eligible for cryotherapy
    - Screen with VIA and treat with cryotherapy, or LEEP when not eligible for cryotherapy

- Screen with an HPV test followed by colposcopy (with or without biopsy) and treat with cryotherapy, or LEEP when not eligible for cryotherapy
- Screen with cytology followed by colposcopy (with or without biopsy) and treat with cryotherapy or LEEP (when not eligible for cryotherapy)

Scope

Disease/Condition(s)

- Precancerous lesions
- Cervical intraepithelial neoplasia (CIN)
- Cervical cancer

Note: It should be noted that these guidelines focus on cervical screening to detect precancerous lesions in order to allow early treatment and thus prevent these from evolving into cancerous lesions. These guidelines do not address primary prevention of cervical cancer through vaccination against human papillomavirus (HPV).

Guideline Category

Prevention

Screening

Treatment

Clinical Specialty

Family Practice

Infectious Diseases

Obstetrics and Gynecology

Oncology

Preventive Medicine

Intended Users

Advanced Practice Nurses

Allied Health Personnel

Health Care Providers

Nurses

Other

Physician Assistants

Physicians

Public Health Departments

Guideline Objective(s)

- To provide recommendations for strategies for screen-and-treat strategies to prevent cervical cancer
- To assist decision-makers to determine whether to provide a different screening test followed by a different treatment, or to provide a series of tests followed by an adequate treatment

Target Population

Women 30 years of age (recommended age to start screening) and older because of their higher risk of cervical cancer

Interventions and Practices Considered

Screening

1. Human papillomavirus (HPV) test alone
2. Visual inspection with acetic acid (VIA) alone
3. HPV test followed by VIA
4. Cytology or HPV test followed by colposcopy (with or without biopsy)

Treatment

1. Cryotherapy
2. Loop electrosurgical excision procedure (LEEP)

Major Outcomes Considered

- Mortality from cervical cancer
- Cervical cancer incidence
- Detected cervical intraepithelial neoplasia (CIN)2, CIN3 (collectively referred to as CIN2+)
- Major infections (requiring hospital admission and antibiotics, e.g., pelvic inflammatory disease)
- Maternal bleeding
- Premature delivery
- Fertility
- Identification of sexually transmitted infections (benefit)
- Minor infections (requiring outpatient treatment only)

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

The Methods Group (MG) searched the MEDLINE and EMBASE online databases up to February 2012 for screening strategies related to a human papillomavirus (HPV) test compared to visual inspection with acetic acid (VIA), and VIA compared to cytology. A separate search was conducted to update a Cochrane Review that was in progress for an HPV test compared to cytology up to November 2012. Another search was conducted for colposcopy up to September 2012 (see Annex 5 in the original guideline document for search strategies). The MG used the

evidence on treatment of cervical intraepithelial neoplasia (CIN) that was concurrently being gathered for the development of the *WHO guidelines for treatment of cervical intraepithelial neoplasia 2-3 and adenocarcinoma in situ: cryotherapy, large loop excision of the transformation zone, and cold knife conization* (see the NGC summary). The searches were not restricted by language or study design in order not to exclude primary studies or previously published systematic reviews in this area. Reference lists of relevant studies were reviewed and the World Health Organization (WHO) Guideline Development Group (GDG) was contacted for additional references.

At least two members of the MG independently screened titles and abstracts and the full text of relevant articles, and a third investigator resolved disagreements. The MG included observational studies for diagnostic test accuracy studies considered at low risk of bias. For example, all women in the studies had to receive both screening tests that were being compared, and all women who tested positive or negative (or a random sample of at least 10% of the women who tested negative) had to receive the 'gold standard' diagnostic test. Studies had to include non-pregnant women aged 18 years or older who had not been treated previously for CIN. Women could be of human immunodeficiency virus (HIV)-positive or HIV-negative status or of unknown HIV status.

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist was used to develop the flow diagram for inclusion and exclusion of studies (see Annex 6 in the original guideline document). A list of all studies included in the reviews of diagnostic test accuracy is provided in Annex 7 of the original guideline document.

Number of Source Documents

A total of 1894 were identified for screening tests and 1925 for colposcopy. Full-text articles assessed for eligibility included 178 for screening tests and 219 for colposcopy. There were 31 studies included in the meta-analysis, and 1 duplicate study.

See Annex 6 of the original guideline document for the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagrams for inclusion and exclusion of studies for evidence reviews.

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Grading of Recommendations Assessment, Development and Evaluation (GRADE) Categories of Quality of Evidence

High (++++): Further research is very unlikely to change confidence in the estimate of effect.

Moderate (+++0): Further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate.

Low (++00): Further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate.

Very low (+000): The Guideline Development Group (GDG) is very uncertain about the estimate.

Methods Used to Analyze the Evidence

Decision Analysis

Meta-Analysis

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Two members of the Methods Group (MG) independently abstracted data about patient characteristics, setting, and diagnostic test accuracy, using a pre-tested data abstraction form. Data to assess the quality of the studies was also collected with the QUADAS tool (Quality Assessment for Diagnostic Accuracy Studies). The diagnostic test accuracy data were pooled by using Stata 12 data analysis and statistical software.

The MG developed a mathematical model to calculate the benefits and harms of each screen-and-treat strategy compared to other screen-and-treat strategies for women of unknown human immunodeficiency virus (HIV) status and for women of HIV-positive status. Cervical intraepithelial neoplasia (CIN)2 or 3 (collectively referred to as CIN2+) prevalence, natural progression data, the pooled diagnostic test accuracy results, and pooled data on treatment effects and complications were all considered in the model (see Annex 7 in the original guideline document for references used in the model). The estimates of the expected absolute effects on health-care outcomes and a summary of the model assumptions are provided transparently in the evidence profiles for women of negative or unknown HIV status and for women of HIV-positive status (see Supplemental material, Sections A and B [see the "Availability of Companion Documents" field]) and for women of different ages.

Two members of the MG evaluated the quality of evidence using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach and presented the evidence and its quality in the GRADE evidence profiles. Evidence for diagnostic accuracy of the screening tests is presented in evidence profiles for diagnostic test accuracy for each recommendation (see Supplemental material, Sections A and B, generally in Section 2.1 for each recommendation). The evidence from the model (i.e., outcomes after a screen-and-treat strategy) is also presented in evidence profiles (see Supplemental material, Sections A and B, generally in Sections 2.2 and 2.3 for each recommendation, according to age). The quality of the evidence or confidence in the effect estimates was assessed as high, moderate, low, or very low, according to the GRADE criteria (see the "Rating Scheme for the Strength of the Evidence" field). Tables to facilitate decision-making for recommendations (evidence-to-recommendations tables) were produced for each recommendation. These tables include a summary of the evidence (benefits and harms), an assessment of the quality of the evidence, relevant patient values and preferences, and any implications for use of resources and feasibility (see Supplemental material, Sections A and B).

Modelling of Health Outcomes

A screening test with the highest diagnostic accuracy is not necessarily the test of choice in clinical practice. The decision to recommend a screening test needs to be justified by its impact on downstream patient-important health outcomes. Decision analysis is a powerful tool for evaluating a diagnostic or screening test on the basis of long-term patient-important outcomes when only intermediate outcomes – such as test sensitivity and specificity – are known. When making the decision to recommend a diagnostic or screening test, a panel should consider the health outcomes downstream from the test. For example, the health risks of interventions resulting from false-positive (FP) and false-negative (FN) findings should be compared with the health benefits associated with true-negative (TN) and true-positive (TP) findings.

To inform these recommendations, the expert panel built a mathematical model using TreeAge Pro 2012 software. In this model the panel calculated the proportions of TP, TN, FP and FN findings for each of the screening tests (visual inspection with acetic acid [VIA], human papillomavirus [HPV] and cytology) given the pooled test-accuracy estimates and the pretest probability of having CIN in that population. The panel then calculated the probability of developing any of the critical outcomes for decision-making (see Box 2 in the original guideline document and the "Major Outcomes Considered" field) based on the treatment they may receive and the pooled estimates of efficacy and potential complications of the different treatments (cryotherapy, cold knife conization [CKC] and loop electrosurgical excision procedure [LEEP]). To calculate an overall estimate of the outcome, the panel added the probability of developing an outcome for each of the categories (TP, TN, FP, FN) for the same screening test and treatment option. The panel identified the assumptions for the models a priori. These assumptions are summarized in the Supplemental material available online, Sections A and B (below each GRADE evidence table for patient-important outcomes following different screen-and-treat strategies) (see the "Availability of Companion Documents" field). The panel also specified a priori the sensitivity analysis they performed based on HIV status (HIV-positive compared to unknown HIV status) and different age categories.

Methods Used to Formulate the Recommendations

Expert Consensus (Consensus Development Conference)

Description of Methods Used to Formulate the Recommendations

The methods used to develop these guidelines followed the *WHO handbook for guideline development* (see the "Availability of Companion Documents" field).

Guideline Groups

The World Health Organization (WHO) formed a Guideline Development Group (GDG) for the screen-and-treat strategies to prevent cervical cancer. The 17 selected members provided expert clinical guidance and support throughout the guideline development process. WHO also selected an External Review Group (ERG) comprising 33 professionals, including health-care providers with experience in screening and treating cervical intraepithelial neoplasia (CIN), pathologists, researchers in cervical cancer prevention and treatment, programme directors, health

educators, epidemiologists, public health officers, nurses and methodologists. A Methods Group (MG) from the MacGRADE Centre at McMaster University, a WHO collaborating centre, provided expertise in evidence synthesis and guideline development processes.

Formulating Questions and Determining Outcomes

In February 2011, the GDG met to discuss the questions and outcomes to address in the chapter on screen-and-treat strategies to appear in the updated *Comprehensive cervical cancer control: a guide to essential practice* (C4-GEP), in order to incorporate new evidence. The GDG identified 15 potential questions to guide the evidence review for screening options and treatment strategies for cervical pre-cancer. The MG surveyed the GDG anonymously online using Survey Monkey to prioritize the questions and determine which ones are clinically relevant or used in practice; 14 out of 17 members responded. Among the 15 questions, the GDG identified 7 that related to comparisons between standard screen-and-treat strategies and those that are NOT typically used in practice (e.g., a human papillomavirus [HPV] test followed by cytology), and therefore these seven questions were excluded. The remaining eight questions were retained as the basis for the screening recommendations (see Box 1 in the original guideline document).

During this same meeting, the GDG developed a list of outcomes that should be considered when making decisions and recommendations for the screen-and-treat strategies. These outcomes were informed by the work previously conducted for the preparation of the WHO guidelines entitled *Use of cryotherapy for cervical intraepithelial neoplasia* (see the NGC summary). Following the meeting, the MG surveyed all GDG and ERG members online using Survey Monkey to identify and rank the critical outcomes for making recommendations. Participants ranked outcomes on a scale from 1 (not at all important) to 7 (critical) in terms of importance for decision-making. Thirty of the 50 members surveyed provided responses and an average ranking was calculated for each outcome. Outcomes with an average ranking of 4 (important) or higher were included in the evidence review and considered when making the recommendations (see Box 2 in the original guideline document and the "Major Outcomes Considered" field).

Development of Recommendations

In early 2012 (26–28 April), the GDG, the ERG and the MG met to discuss the recommendations. One member each from the GDG and the MG chaired the meeting, which was attended by experts from around the world, representing various public health and medical disciplines. To expand the geographical representativeness of the GDG, it was decided that the ERG – a large group with members representing many countries – would participate in the development of the recommendations during that meeting. Members of the MG presented evidence profiles and evidence-to-recommendation tables, which included evidence about the benefits and harms, values and preferences, resources and feasibility.

With regard to patient values and preferences, the GDG agreed that the evidence found could be applied across all recommendations. The evidence from qualitative studies suggests that women may fear screening and may have a high level of anxiety related to colposcopy or treatment, and may feel burdened by the need for a second visit for treatment. However, once women decide to be screened they find the screening tests and immediate treatment acceptable. Evidence from the systematic reviews demonstrated that there is a preference for more frequent screening and active management among women who have screened positive for CIN1. In addition, evidence from controlled trials showed that women find treatment by cryotherapy and loop electrosurgical excision procedure (LEEP) acceptable, and are satisfied with a screen-and-treat approach.

WHO has recently developed the *WHO cervical cancer prevention and control costing tool*. This tool includes two modules: one on the cost of a HPV vaccination and the other on the cost of a screen-and-treat programme. The purpose of the tool is to help programme managers develop a budget for the programme. In order to develop the tool, the cost of each intervention was collected for a range of countries and the calculation tables were developed. This, in addition to the experience of the members of the ERG, was essential to the discussion of the resources needed for each of strategy.

Recommendations were made by the GDG and ERG by balancing the overall desirable and undesirable consequences of the screen-and-treat strategies, which included consideration of important outcomes, values and preferences, resources and feasibility, along with the level of certainty of that information. Members of the panel made decisions based on consensus and unanimous voting, which was not anonymous. The results of those discussions are documented in the evidence-to-recommendation tables for each recommendation, in the Supplemental material, Sections A and B (see the "Availability of Companion Documents" field). The GDG and ERG also identified key research gaps. All the discussions and decisions took place during the April 2012 meeting and no major discord was noted.

The recommendations were assessed as 'strong' or 'conditional', in accordance with the *WHO handbook for guideline development* (see the "Rating Scheme for the Strength of the Recommendations" field). Strong recommendations have been worded as 'The GDG recommends' and conditional recommendations as 'The GDG suggests'. A strong recommendation means that it was clear to the panel that the net desirable consequences of the specified strategy outweighed those of the alternative strategy. But a conditional recommendation was made when it was less clear whether the net desirable consequences of the specified strategy outweighed those of the other strategy. In this guideline, many recommendations are conditional.

Rating Scheme for the Strength of the Recommendations

Strength of Recommendations

- Strong: A strong recommendation means that it was clear to the panel that the net desirable consequences of the specified strategy outweighed those of the alternative strategy.
- Conditional: A conditional recommendation was made when it was less clear whether the net desirable consequences of the specified strategy outweighed those of the other strategy.

Interpretation of Strong and Conditional Recommendations

Implications	Strong recommendation "The expert panel recommends… "	Conditional recommendation "The expert panel suggests… "
For patients	Most individuals in this situation would want the recommended course of action, and only a small proportion would not. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.	The majority of individuals in this situation would want the suggested course of action, but many would not.
For clinicians	Most individuals should receive the intervention. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator.	Clinicians should recognize that different choices will be appropriate for each individual and that clinicians must help each individual arrive at a management decision consistent with his or her values and preferences. Decision aids may be useful to help individuals make decisions consistent with their values and preferences.
For policymakers	The recommendation can be adopted as policy in most situations.	Policy-making will require substantial debate and involvement of various stakeholders.

Cost Analysis

The World Health Organization (WHO) has recently developed the *WHO cervical cancer prevention and control costing tool*. This tool includes two modules: one on the cost of a human papillomavirus (HPV) vaccination and the other on the cost of a screen-and-treat programme. The purpose of the tool is to help programme managers develop a budget for the programme. In order to develop the tool, the cost of each intervention was collected for a range of countries and the calculation tables were developed. Refer to the "Resource implications" sections of the Supplemental Material (see the "Availability of Companion Documents" field) for judgements on each recommendation made by the expert panel.

Method of Guideline Validation

External Peer Review

Internal Peer Review

Description of Method of Guideline Validation

Guideline Review and Approval Process

The World Health Organization (WHO) screen-and-treat strategies to prevent cervical cancer underwent the following peer review process before and during development:

- The questions formulated for the development of the guidelines were circulated among the WHO Steering Group, who also discussed them with the Guideline Development Group (GDG). When the GDG and the WHO Steering Group had reached agreement on the questions, these were sent to the External Review Group (ERG).
- The protocol for systematic reviews was circulated among the GDG. This protocol was also discussed during the ERG meeting, which was also attended by the European Guidelines Development Group in addition to the WHO Steering Group, the GDG and the Methods Group (MG). During that meeting the evidence that had been identified and the draft evidence profiles were discussed.
- Discussions and conference calls were regularly held with the GDG to discuss the data from the literature review, the models, the estimated parameters to include in the models, and the outcomes.
- The final draft guideline with the recommendations was circulated among the members of the GDG for review before WHO clearance.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for each recommendation (see the "Major Recommendations" field).

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

The goal of a screen-and-treat programme for cervical cancer is to reduce cervical cancer and related mortality with relatively few adverse events.

See the "Remarks" and "Summary of the evidence" sections of the original guideline document as well as the supplemental material for details on the balance of benefits versus harms of specific interventions (see the "Availability of Companion Documents" field).

Potential Harms

- Health risks of interventions resulting from false-positive (FP) and false-negative (FN) findings
- Overtreatment may be slightly greater with a human papillomavirus (HPV) test when compared with cytology followed by colposcopy without biopsy (7/100 more women) or with biopsy when indicated (10/100 more women). This may result in slightly more complications with the HPV test strategy.
- Overtreatment may be slightly greater with visual inspection with acetic acid (VIA) compared to cytology followed by colposcopy without biopsy (11/100 more women) or with biopsy when indicated (18/100 more women). This may result in slightly greater harm with the VIA strategy.
- Overtreatment may be slightly greater with an HPV test only compared with an HPV test followed by colposcopy without biopsy (5/100 more women) or with biopsy when indicated (12/100 more women). This may result in slightly greater harm with an HPV-test-only strategy. The evidence for women of human immunodeficiency virus (HIV)-positive status showed that there is likely to be an even greater rate of cervical intraepithelial neoplasia (CIN)2 and CIN3 (collectively referred to as CIN2+) recurrences with an HPV test followed by VIA (22/1000 more), as well as more cervical cancers (17/10,000 more) and more deaths (12/100,000 more) than with HPV only.

See the "Remarks" and "Summary of the evidence" sections of the original guideline document as well as the supplemental material for details on the balance of benefits versus harms of specific interventions (see the "Availability of Companion Documents" field).

Qualifying Statements

Qualifying Statements

- The designations employed and the presentation of the material in this publication do not imply the expression of any opinion whatsoever on the part of the World Health Organization (WHO) concerning the legal status of any country, territory, city or area or of its authorities, or

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- The best evidence to assess the effects of a screen-and-treat strategy is from randomized controlled trials in which women are randomly allocated to receive one or another screen-and-treat strategy and then all screened women are followed and patient-important health outcomes – such as cervical intraepithelial neoplasia (CIN) recurrence, cervical cancer and complications of treatment – are measured. The expert panel identified few randomized controlled trials that evaluated screen-and-treat strategies and patient-important outcomes. In particular, there were very few studies that assessed the strategies that the Guideline Development Group (GDG) ranked as clinically relevant (e.g., human papillomavirus [HPV] test followed by visual inspection with acetic acid [VIA]). In fact, few studies were found, randomized controlled trials or otherwise, that assessed a sequence of tests, such as an HPV test followed by VIA. There were also few studies that assessed the accuracy of diagnostic tests or reported on patient outcomes in women who are human immunodeficiency virus (HIV)-positive or at high risk of being HIV-positive. See "Research gaps and further considerations" in the original guideline document for additional discussion of guideline limitations.

Implementation of the Guideline

Description of Implementation Strategy

Guideline Dissemination

These guidelines will be available online at the World Health Organization (WHO) Library database and there will be a link on WHO's Sexual and Reproductive Health Web page and in the *WHO Reproductive Health Library (RHL)*, an electronic review journal. Many of these organizations will also copy the announcement in their newsletters. The publication will also be announced in the United Nations Development Programme (UNDP)/United Nations Population Fund (UNFPA)/United Nations Children's Fund (UNICEF)/WHO/World Bank Special Programme of Research, Development and Research Training in Human Reproduction (HRP) WHO Reproductive Health Update, which reaches more than 2000 subscribers and numerous organizations with whom WHO is working. Many of these organizations will also copy the announcement in their newsletters.

The guidelines will be distributed in print to subscribers to WHO publications, to the WHO mailing list for mandatory free distribution (national chief health executives, ministers of health or director-generals of health, depository libraries for WHO publications, WHO representatives/liaison officers, WHO/HQ library, WHO regional offices, and off-site office libraries), additional non-mandatory free recipients (competent national authorities for sexual and reproductive health, cancer control programmes, national research centres in reproductive health, and WHO collaborating centres), WHO staff at headquarters, regional and country offices and elsewhere, concerned non-governmental organizations (NGOs), medical societies concerned with cancer control and/or sexual and reproductive health, scientific journals (including general medical journals and journals specialized on sexual and reproductive health or cancer), international organizations, and donors, potential donors, potential publishers of translated versions, as well as all those who contributed to the documents.

Conference invitations to discuss and present the guidelines will be accepted.

Regional conferences are already planned in the Americas and Africa to present the new recommendations to a number of stakeholders involved in national programme planning in 2013. The other regions will be covered in 2014.

If requested by regional offices, countries will be supported to adapt the guideline to their country-specific needs and to integrate the material with existing national guidelines. Adaptation will be done by organizing regional, sub-regional and country-level workshops for discussion of each recommendation, in order to adapt them to the national epidemiologic, cultural, and socioeconomic context.

Initially, the guidelines will be available in English only and translations will be developed subject to the availability of funding. Translation into non-UN languages and publication in these languages by third parties will be encouraged.

Implementation Tools

Clinical Algorithm

Foreign Language Translations

Resources

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

Staying Healthy

IOM Domain

Effectiveness

Patient-centeredness

Identifying Information and Availability

Bibliographic Source(s)

World Health Organization (WHO). WHO guidelines for screening and treatment of precancerous lesions for cervical cancer prevention. Geneva (Switzerland): World Health Organization (WHO); 2013. 40 p. [20 references]

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2013

Guideline Developer(s)

World Health Organization - International Agency

Source(s) of Funding

The Flanders International Cooperation Agency (FICA), the Institut National du Cancer (INCa), France, and the GAVI Alliance (formerly the Global Alliance for Vaccines and Immunisation) provided the main funding for this document.

Guideline Committee

Guidelines Development Group

World Health Organization (WHO) Steering Group

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Financial Disclosures/Conflicts of Interest

Management of Conflicts of Interest

Conflicts of interest were managed as follows:

1. All experts who participated in the process were required to complete the World Health Organization (WHO) Declaration of Interest (DOI) form before they commenced their work for WHO, and to promptly notify WHO if any change in the disclosed information occurred during the course of this work. The completed DOI forms were reviewed by the WHO Secretariat with a view to managing disclosed interests in the field of cervical cancer screening and treatment.
2. At the meeting of the External Review Group (ERG) in September 2010 and at the first joint meeting of the Guideline Development Group (GDG), Methods Group (MG) and the ERG in 2013, each expert disclosed his/her declared interests to the other experts as part of the round of introductions at the beginning of the meeting so that the group was aware of any existing interests among the members.
3. All declared interests have been reviewed by WHO's Office of the Legal Counsel. The decision was that all experts could participate in the process but interests should be disclosed in the guideline.
4. All relevant declared interests (15 out of 54 experts) are summarized in this report (see Annex 1 in the original guideline document).

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Guideline Availability

Electronic copies: Available in English, French, and Spanish from the World Health Organization (WHO) Web site.

Print copies: Available from the WHO Press, World Health Organization, 20 Avenue Appia, 1211 Geneva 27, Switzerland; Phone: +41 22 791 3264; Fax: +41 22 791 4857; E-mail: bookorders@who.int.

Availability of Companion Documents

The following are available:

- WHO handbook for guideline development. Geneva (Switzerland): World Health Organization (WHO); 2012. 56 p. Electronic copies: Available from the World Health Organization (WHO) Web site.
- WHO guidelines for screening and treatment of precancerous lesions for cervical cancer prevention. Supplemental material: GRADE evidence-to-recommendation tables and evidence profiles for each recommendation. Geneva (Switzerland): World Health Organization (WHO); 2013. 194 p. Electronic copies: Available from the WHO Web site.
- WHO cervical cancer prevention and control costing (C4P) tool user's guide. Geneva (Switzerland): World Health Organization; May 2012. 34 p. Electronic copies: Available in English and French from the WHO Web site.

Patient Resources

None available

NGC Status

This NGC summary was completed by ECRI Institute on September 15, 2015.

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